

Demographic data, [123 I] IBZM SPECT, and bradykinesia pegboard test in patients with writer's cramp and controls

	Age (y)	Duration of disease (y)	[123 I] IBZM SPECT		Pegboard (s)	
			R brain	L brain	R hand	L hand
Writer's cramp (n = 10)†	51.6 (9.0)	8.6 (3.9)	1.56 (0.10)***	1.53 (0.09)***	9.7 (1.1)	9.8 (0.9)
Controls (n = 12)	51.8 (11.0)	—	1.88 (0.19)	1.87 (0.15)	—	—
Controls (n = 46)	55.8 (9.5)	—	—	—	9.8 (1.5)	10.0 (1.4)

Values in parentheses are SD.

***P < 0.0001 v controls.

†Four patients had simple writer's cramp and six had dystonic writer's cramp.

possible involvement of dopaminergic striatal receptors in dystonia, we measured the availability of striatal D2 receptors in patients with writer's cramp using [123 I]IBZM SPECT.

Ten consecutive right handed patients (eight male and two female) were classified into four with simple and six with dystonic writer's cramp depending on whether or not the symptoms appeared only during writing. None of the patients had been treated with neuroleptic, dopaminergic, or anticholinergic drugs or botulinum toxin. Hypokinesia, rigidity, and resting tremor were absent in all patients. Bradykinesia of the hands was assessed with a pegboard test, measuring the time (s) required to invert eight pegs. Pegboard performance of patients was compared with that of 46 age matched controls. Results from [123 I]IBZM SPECT were compared with 12 other age matched controls from an earlier study.²

A brain dedicated SPECT system, the Strichman Medical Equipment 810X, was used. Two hours after intravenous injection of approximately 185 MBq [123 I]IBZM (Cygne BV, Technical University, Eindhoven), tomographic SPECT studies were performed. A maximum of 12 slices was made, starting at the orbitomeatal line and proceeding parallel to it (300 s/slice; inter-slice distance 10 mm). For analysis of specific striatal [123 I]IBZM binding, two slices with the highest striatal activity were summed and a template with fixed regions of interest for the striatum and occipital cortex was placed bilaterally on the summated image.² The ratio of the striatal binding divided by the occipital binding quantifies specific binding.

The mean ages (table) did not differ among the three groups (*t* tests). Left and right [123 I]IBZM striatal : occipital ratios were significantly lower in patients than in controls (*t* test, *P* < 0.000). There was no asymmetry between [123 I]IBZM ratios for the hemispheres in patients or controls (repeated measures multivariate analysis of variance (MANOVA) tests involving side, group, and group by side: *P* > 0.05). The pegboard test did not differ between patients with writer's cramp and controls in either hand (*t* tests), showing that the patients with writer's cramp did not have bradykinesia. There was no correlation between age or duration of disease and [123 I]IBZM ratios (Pearson's correlation coefficients). None of the variables differed between patients with simple and dystonic writer's cramp.

Our results suggest that the striatal dopaminergic system is involved in writer's cramp given that patients with writer's cramp have a significantly lower level of striatal [123 I]IBZM binding than controls. Unfortunately, lack of an accurate measure of the severity of writer's cramp itself prevented us from studying the relation between severity of dystonia and [123 I]IBZM. We did not find a correlation between [123 I]IBZM ratios and duration of disease or

age. This probably means that the decline in striatal D2 receptors is not linearly progressive but remains stable over many years, which accords with our clinical impression. However, because the preclinical [123 I]IBZM ratios of the individual patients were not known, it is hazardous to assess rates of decline in a small cross sectional sample.

The results raise some questions. Firstly, there was bilateral reduction of available striatal D2 receptors, whereas the symptoms were unilateral and there was no asymmetry between the hemispheres. Bilateral abnormalities in writer's cramp, have, however, also been found by others.^{1,3} This bilaterality probably only means that the abnormalities found are related to particular motor dysfunctions which pass undetected if not properly challenged, as shown by the fact that many patients develop writer's cramp on the left side, if they change to writing with the left hand. Accordingly, it is also not uncommon to find involvement of the left, or finger-hand, in musicians playing keyboards, guitars, or other stringed instruments.³

A second question is why the reduced availability of D2 receptors was not accompanied by parkinsonism in our patients. According to well known models of basal ganglia function, overactivity of the indirect striatopallidal pathway is usually associated with parkinsonism. Because D2 receptor stimulation inhibits the indirect pathway, by contrast with the D1 receptor driven direct pathway,⁴ the decreased striatal D2 receptor binding in writer's cramp indicates disinhibition of the indirect pathway which might be expected to be accompanied by parkinsonism. In line with this view, we found the mean [123 I]IBZM ratio to be 1.43 (SD 0.16) in patients with definite hypokinetic-rigid symptoms due to multiple system atrophy or progressive supranuclear palsy,² which is in the same range as the values obtained in most of the present patients with writer's cramp (1.27–1.59).

Therefore, our finding is probably better explained by loss of D2 receptors on cholinergic striatal interneurons rather than D2 receptors on striatal spiny output neurons. The number of D2 receptors on striatal cholinergic interneurons is sufficient to account for the decreased density of D2 receptors in our patients.⁵ Furthermore, striatal cholinergic interneurons are highly represented in the sensorimotor part of the striatum and are predominantly innervated by fibres from the thalamus suggesting a feed forward modulation from thalamus to striatum.⁶ A dysfunction of such thalamo-striatal sensorimotor function—caused by increased activity of striatal cholinergic interneurons resulting from disinhibition due to D2 receptor loss—fits the suggestion that central sensory processing in dystonia is impaired.⁷ Our hypothesis that writer's cramp dystonia could be related to an increased activity of striatal cholinergic interneurons is also consistent with the increased density of striatal cholinergic

interneurons in dystonia after perinatal asphyxial injury,⁸ and with the well known efficacy of anticholinergic therapy in dystonia.

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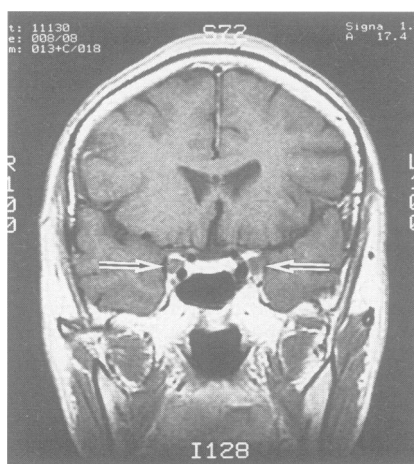
- 1 Tempel LW, Perlmuter JS. Abnormal cortical responses in patients with writer's cramp. *Neurology* 1993;43:2252–7.
- 2 van Royen E, Verhoeff NF, Speelman JD, Wolters EC, Kuiper MA, Janssen AG. Multiple system atrophy and progressive supranuclear palsy. Diminished striatal D2 dopamine receptor activity demonstrated by 123I-IBZM single photon emission computed tomography. *Arch Neurol* 1993;50:513–6.
- 3 Ikoma K, Samii A, Mercuri B, Wassermann EM, Hallett M. Abnormal cortical motor excitability in dystonia. *Neurology* 1996;46:1371–6.
- 4 Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma FJ Jr, Sibley DR. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* 1990;250:1429–32.
- 5 Dawson VL, Dawson TM, Wamsley JK. Muscarinic and dopaminergic receptor subtypes on striatal cholinergic interneurons. *Brain Res Bull* 1990;25:903–12.
- 6 Kawaguchi Y, Wilson CJ, Augood SJ, Emson PC. Striatal interneurons: chemical, physiological and morphological characterisation. *TINS* 1995;18:527–35.
- 7 Hallett M. Is dystonia a sensory disorder? *Ann Neurol* 1995;38:139–40.
- 8 Burke RE, Karanas AL. Quantitative morphological analysis of striatal cholinergic neurons in perinatal asphyxia. *Ann Neurol* 1990;27:81–8.

Chronic sensory ataxic neuropathy and ophthalmoplegia with oculomotor nerve hypertrophy associated with IgM antibodies against gangliosides containing disialosyl groups

Recent studies have shown that serum anti-ganglioside antibodies may be involved in various immune mediated peripheral neuropathies. We report an investigation of anti-ganglioside antibodies in a patient with chronic sensory neuropathy and ophthalmoplegia associated with oculomotor nerve hypertrophy.

A 40 year old man had been in good health when he developed subacute diplopia in 1987. At the age of 45, he developed a moderately unsteady gait after an infection of the upper respiratory tract. The symptom gradually worsened and he was unable to run at the age of 46. At the age of 48, he was admitted to hospital because of progressive numbness in all limbs and difficulty in performing fine motor movements. Treatment

included high dose intravenous steroid and immune absorption plasmapheresis. Because he did not improve, he was transferred to our hospital. There was no family history of neuropathy or other systemic diseases. On admission, he had anisocoria (right 2.5 mm, left 3.5 mm), and light reflexes were absent on both sides. Ocular movement was impaired in all directions. The other cranial nerves were intact. Muscle power in the limbs was normal and there was no muscular atrophy. All deep tendon reflexes and Babinski's sign were absent. Touch, cold, and pinprick sensations were slightly impaired in his hands and feet, but not in his face and trunk. There was profound loss of position and vibration senses in all limbs. The patient had pseudoathetosis of the upper limbs. A finger-nose test showed dysmetria with terminal tremor in both sides. He could not sit up in bed due to severe truncal ataxia. Autonomic functions were intact. Routine laboratory tests and concentrations of IgM and other immunoglobulins were normal. Serum immunoelectrophoresis did not show monoclonal gammopathy. The titre of cold agglutinin was not raised. There was no CSF pleocytosis and CSF protein content was 275 mg/dl (IgG 11.9%, normal; 2%–5%). Brain MRI showed hypertrophy of both oculomotor nerves with no gadolinium enhancement (figure). The EEG was normal. Motor nerve conduction studies showed prolonged F wave latencies (39.6 ms, control 25.4 (SD 1.4 ms) with decreased amplitude of compound muscle action potentials (2.3 mV, control 9.5 (SD 3.2 mV) in the right median nerve and prolonged F wave latencies (67.5 ms, control 44.4 (SD 3.4 ms) with reduced motor conduction velocity (36 m/s, control 49 (SD 3 ms) in the right tibial nerve. Sensory nerve conduction studies in the right median and sural nerves showed decreased amplitude of sensory nerve action potentials (SNAPs) and reduced conduction velocities (median nerve; SCV 24 m/s, SNAP 0.9 mV, sural nerve; SCV 38 m/s, SNAP 0.9 mV). An EMG showed mild chronic partial denervation in all limbs. Sural nerve biopsy showed a decreased density of large myelinated fibres (density of myelinated fibres: total 8721/mm², 5 μ m \geq 138/mm², 5 μ m \leq 8563/mm², control; total 8500 (SD 650)/mm², 5 μ m \geq 3080 (SD 462)/mm², 5 μ m \leq 5412 (SD 332)/mm², associated with several thinly myelinated axons. Some fibres showed myelin ovoid degeneration. A few onion bulb formations were noted. There was subperineurial oedema in some fascicles. In teased fibre preparations, the frequency of fibres with segmental demyelination with remyelination was 6%, with axonal degeneration in 20%, and remyelination without demyelination in 10%. The severe truncal ataxia and ophthalmoplegia improved after double filtration plasmapheresis. However, his symptoms gradually worsened three months later with increases in several antiganglioside antibodies. A combination of prednisolone and azathioprine



Gadolinium enhanced coronal T1 weighted image. Note hypertrophy of bilateral oculomotor nerve without enhancement (arrow)

treatment was not effective. Antiglycolipid antibodies were investigated by enzyme linked immunostaining as previously described.¹ Antigens used in enzyme linked immunosorbent assay (ELISA) were GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, galactocerebroside (Gal-C), and asialo GM1. ELISA showed IgM antibody activities against GD1b, GD3, GT1b, and GQ1b in the patient's serum, but not IgG antibody activities against any of the gangliosides. The reactivity was also detected by thin layer chromatography and immunostaining. Although the antibody titres decreased after plasmapheresis, the titres rose again at the time of exacerbation, three months after plasmapheresis.

This unusual case has features of both chronic sensory ataxic neuropathy and ophthalmoplegia. Considering the effectiveness of plasmapheresis, the pathophysiological mechanism may be immune mediated. IgM M proteins binding to several gangliosides with disialosyl residues, such as GD1b, GD3, GT1b, and GQ1b, have been detected specifically in serum samples from patients with sensory ataxic neuropathy.² The present patient had serum IgM antibody with reactivities to GD1b and other gangliosides with disialosyl residues, although no IgM M protein was detected. Preliminary incubation with GD1b, GD3, and GT1b, performed as previously described³ reduced the antibody activities against all four gangliosides (data not shown). It suggests that the same IgM antibody, which may recognise the disialosyl residue, binds to all four gangliosides. This antibody reactivity may play an important part in chronic sensory ataxic neuropathy in this patient.

The most interesting feature of this patient is ophthalmoplegia with oculomotor nerve hypertrophy. Although focal cranial nerve involvement has been shown in chronic immune mediated neuropathy, ocu-

lomotor nerve hypertrophy has not been previously reported. There was no gadolinium enhancement of either oculomotor nerve, suggesting that the appearance on MRI is likely related to increased connective tissue elements and Schwann cell proliferation as a consequence of chronic inflammation. Recently, Chiba *et al* found that IgG antibody against GQ1b was specifically raised in acute phase serum samples from patients with Miller Fisher syndrome³ and Guillain-Barré syndrome with ophthalmoplegia.⁴ Anti-GQ1b antibody is therefore considered to be specifically associated with ophthalmoplegia in both diseases. Because GQ1b is rich in the paranodal regions of oculomotor, trochlear, and abducens nerves,⁴ anti-GQ1b antibody might be involved in the pathogenic mechanism of ophthalmoplegia by binding to these regions. Although IgM M protein binding to gangliosides with disialosyl residues such as GQ1b has been reported, the patients usually did not have ophthalmoplegia. This may be due to the difference in the class and specificity of the antibody; anti-GQ1b antibody in Miller Fisher syndrome and Guillain Barré syndrome with ophthalmoplegia is of the IgG class and cross reactions with gangliosides such as GD1b, GD3, and GT1b are rare. There is one reported patient with IgM paraproteinaemic sensory ataxic neuropathy with transient ophthalmoplegia.² IgM M protein of that patient bound to gangliosides with a disialosyl residue but the reactivity with GQ1b was not examined. In the present patient, we confirmed IgM reactivity with GQ1b, which might account for the pathophysiological mechanism of ophthalmoplegia and oculomotor nerve hypertrophy.

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- 1 Kusunoki S, Chiba A, Kon K, *et al*. N-acetyl-galactosaminyl GD1a is a target molecule for serum antibody in Guillain-Barré syndrome. *Ann Neurol* 1994;35:570–6.
- 2 Ilyas AA, Quarles RH, Dalakas MC, *et al*. Monoclonal IgM in a patient with paraproteinemic neuropathy binds to gangliosides containing disialosyl groups. *Ann Neurol* 1985;18:655–9.
- 3 Chiba A, Kusunoki S, Shimizu T, Kanazawa I. Serum IgG antibody to ganglioside GQ1b is a possible marker of Miller Fisher syndrome. *Ann Neurol* 1992;31:677–9.
- 4 Chiba A, Kusunoki S, Obata H, Machinami R, Kanazawa I. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: clinical and immunohistochemical studies. *Neurology* 1993;43:1911–7.